UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/612,929	04/30/96	HOLMES S	P50186-2

18M1/0509

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EXAMINER	
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ART UNIT	PAPER NUMBER
1806	

DATE MAILED: 05/09/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/612,929	Applicant(s) Holmes et al
	Examiner Sheela J. Huff	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Jan 13, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-38* is/are pending in the application.

Of the above, claim(s) *12, 13, and 19-29* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11, 14-18, and 30-38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3.5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The following errors in the CRF submitted 1/13/97 were corrected by STIC:

STIC edited current application data section with the actual current number: The numbers inputted by the applicant were the prior application data.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-11, 14-18, 30-38, drawn to a fusion protein and methods of using said protein.

Group II, claim(s) 12-13 and 19-29, drawn to nucleic acid sequences.

3. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The product of I is directed to a fusion protein and this product is functionally and structurally different from the nucleic acid sequence of Group II. For example, proteins are mode of amino acids whereas nucleic acid sequences are made of nucleotides and nucleosides. The

product of Group I can be used to make antibodies and screen antibodies whereas the product of Group II cannot.

4. During a telephone conversation with Alissa Eagle on 4/15/97 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-11, 14-18 and 30-38. Affirmation of this election must be made by applicant in responding to this Office action. Claims 12-13 and 19-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-11, 14-18 and 30-38 are pending.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

7. The IDS's filed on 4/26/96 have been made of record. An initialed copy of each of the TPO-1449 is enclosed.

Double Patenting

8. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9. Claims 1-11, 14-17, 30 and 32-38 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-11, 14-17, 30 and 32-38 of copending Application No. 08/483636. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

10. Claims 3 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line 3426A11C1B9. It is not clear that hybridomas possessing the identical properties of the aforementioned cell line are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed hybridoma, a suitable deposit for patent purposes, evidence of public availability of the claimed hybridoma or evidence of the reproducibility without undue experimentation of the claimed hybridoma, is required.

Applicant's referral to the deposit of hybridoma 3426A11C1B9 as disclosed on page 32 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

11. Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in *In Re Colianni*, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals

and Interferences in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986). Among these factors are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the breath of the claims,
5. the amount of direction or guidance present, and
6. the presence or absence of working examples.

The following is an analysis of these factors in relationship to this application.

Nature of the invention

Applicant discloses and claims the use of fusion proteins (antibodies) to treat allergies and other conditions associated with excess IgE production.

State of the Art/Predictability

The claimed invention pertains to the highly experimental and unpredictable field of in vivo therapy using monoclonal antibodies. Articles by Waldmann and Harris are cited in order to establish the general state of the art and level of unpredictability of in vivo human therapy using monoclonal antibodies. The cited references establish that numerous experimental and clinical studies have determined that the effective application of antibody-based therapy methods for in vivo treatment of human diseases has been extremely limited. The complexity and unpredictability of the art to which the invention

pertains provides reasonable basis to question as to the accuracy of applicant's assertion that the antibodies can be used for effective therapy in vivo.

Guidance/Working Examples

Applicant has provided in vitro assays. Those of skill in the art recognize that in vitro assays are useful to screen the effects of agents on target cells. However, in vivo correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay, does not permit a simple extrapolation of in vitro assays to in vivo therapeutic efficacy with any reasonable degree of predictability. In vitro assays depend on cell culture and therefore do not entirely simulate in vivo conditions. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further, an therapeutic agent must accomplish several tasks to be effective. It must be delivered into the circulation and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In the assays, the agent is in contact with cells during the entire exposure period. This is not the case in vivo, where exposure at the target site may be delayed or inadequate. Thus, the in vitro assays are not correlatable to the treatment of allergies and other conditions associated with excess IgE production.

Breadth of the claims

The specification does not teach how to produce and use functional proteins having binding specificity for IL-4 which have the structural elements defined by claim 1. Claims 1-4 require that the claimed fusion protein be comprised of amino acid sequences from only a single CDR. Claims 7 and 8 define fusion proteins which are comprised only of three amino acid sequences of CDRs. It is noted that claims 1-4 do not specify that the amino acid sequences referred to comprise entire CDRs. The claims do not require that any additional elements are present in the antigen-binding regions of the fusion proteins.

The specification only teaches how to produce fusion proteins which comprise the full complement of CDRs characteristic of a non-human donor antibody which are fused in the order in which they exist in the donor antibody, to the framework of a human acceptor antibody. It is known that the sequences and conformations of immunoglobulin CDRs and framework regions are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and fused to appropriate human framework sequences are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human framework sequence, or no framework sequences, would possess the functional characteristics of binding with high affinity to and neutralizing IL-4.

In view of the above, it is the Examiner's position that one skilled in the art could not make and/or use the invention without undue experimentation.

12. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fusion proteins containing the full complement of CDRs, does not reasonably provide enablement for fusion proteins containing only one CDR or CDRs in an unspecified order. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not teach how to produce and use functional proteins having binding specificity for IL-4 which have the structural elements defined by claim 1. Claims 1-4 require that the claimed fusion protein be comprised of amino acid sequences from only a single CDR. Claims 7 and 8 define fusion proteins which are comprised only of three amino acid sequences of CDRs. It is noted that claims 1-4 do not specify that the amino acid sequences referred to comprise entire CDRs. The claims do not require that any additional elements are present in the antigen-binding regions of the fusion proteins. The fusion proteins defined by claims 5-6 comprise a CDR fused to any of the sequences specified in the claims in unspecified combinations.

The specification only teaches how to produce fusion proteins which comprise the full complement of CDRs characteristic of a non-human donor antibody which are fused in the order in which they exist in the donor antibody, to the framework of a human

acceptor antibody. It is known that the sequences and conformations of immunoglobulin CDRs and framework regions are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and fused to appropriate human framework sequences are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions in unspecified order and fused to any human framework sequence, or no framework sequences, would possess the functional characteristics of binding with high affinity to and neutralizing IL-4.

13. Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the binding of antibody to IL-4, does not reasonably provide enablement for the diagnosis of allergies and other conditions associated with excess IgE production.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has demonstrated that monoclonal antibodies can bind to IL-4. However, merely showing that an antibody does not constitute a diagnosis. The samples used in diagnosis are generally tissue samples to blood or serum samples. When used in

assaying these samples, the monoclonal antibody can readily cross-react with one or many of the other proteins present in said sample. Thus, rendering the assay ineffective. Thus one skilled in the art would not readily believe that the monoclonal would solely react with IL-4.

14. Claims 1-11, 14-18 and 30-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In the claims the terminology "is derived from" renders the claim vague and indefinite. The manner of derivation referred to is not known. This phrase is not one which has a single defined meaning in the art nor is it one which is defined in the specification. In the absence of an ascertainable meaning for the phrase, one of skill could not determine the meets and bounds of the claimed subject matter. It is likely that derivation of the subject CDRs would alter the binding characteristics of the resulting fusion protein. Reciting a functional limitation for the CDR in the claim would help overcome this rejection.

b. In the claims, the terminology "neutralizing" renders the claim vague and indefinite. "Neutralizing" what? Which activity of IL-4 is neutralized?

c. In claim 1, the terminology "a first fusion partner" renders the claim vague and indefinite. As defined in the specification, this terminology is a nucleic acid sequence. Thus, it appears that applicant is claiming a nucleic acid sequence (first fusion partner) attached

to a CDR (which is composed of amino acids)? This is not a fusion protein as indicated in the first line of the claim.

d. Claim 2 is vague and indefinite because it is not clear how and where the second fusion partner is attached to the fusion protein.

e. Claim 4 is indefinite in the recitation of a fusion protein wherein a CDR is fused to a second fusion partner which comprises all "or part" of a heavy or light chain or both. It is not known which particular part of the heavy or light chain is referred to. If the portion referred to is a region of the heavy and/or light chain, the characteristics of the constant regions comprising the fusion protein will alter the physical and biological characteristics of the molecule. If the portion referred to is a variable region sequence, the characteristics of the region comprising the fusion protein will affect binding characteristics.

f. Claims 5 and 6 are vague and indefinite because it is not clear what and how the recited sequences are linked or even if they are linked.

g. In claims 5-6 there is no antecedent basis for "said fusion partner sequence".

h. In claims 7-9, there is no antecedent basis for "said amino acid sequences".

I. In claim 8, the first amino acid in Seq ID No. 16 should be lys not leu (see sequence listing). Similar problem is found in claim 11.

j. In claims 7-11 is it unclear if each amino acid sequence are the CDR or part of the CDR. It is also unclear if each sequence can be present three times to give the full complement of CDRs or each only present once?

k. Claims 30-32 are indefinite in the recitation of "high titer". The phrase does not have a defined meaning in the art and thus, one skilled in the art could not determine the meets and bounds of the claims.

l. In claim 37 it is unclear as to what applicant means by "identifying characteristics of 6A1". What characteristics?

j. In claim 31, it is unclear as to what applicant means by "aldehyde-coupled" human IL-4?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 8-9, 11 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 93/04173 (3/4/93).

This reference discloses the sequence of Mae15 light chain as containing the sequence AASNLES (corresponds to SEQ ID No. 18 of the instant application) (see fig. 2). Mae15 is made by recombinant techniques therefore exists in a fusion protein (p. 34-35 and 39). The antibody is used in assay with inherently use a pharmaceutically acceptable

formulation. It is inherent that Mae15 has the ability to neutralize IL-4 with the claimed dissociation constant.

16. Claims 1-4, 14-17, 31-34 and 36 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 93/17106 (9/2/93).

This reference discloses recombinant methods (using fusion proteins) of making humanized antibodies that have the ability to neutralize human IL-4 activity (abstract and pages 41-57). The references discloses humanizing the heavy and or light chains and methods of screening the antibodies for IL-4 activity.

17. Claims 1-2, 4, 8-9, 11, 14 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 327000.

This reference discloses making humanized antibodies (reference calls them chimeric antibodies) wherein the amino acid sequence of the light chain has contains the sequence lys-ala-ser-gln-ser-val-asp-tyr-asp-gly-asp-ser-tyr-met-asn (corresponds to SEQ ID NO. 16 of the instant application) (p. 4, lines 39). This light is made as part of a fusion protein(p. 5 and Examples). The antibody is used in assay which inherently uses a pharmaceutically acceptable formulation. It is inherent that humanized antibodies have the ability to neutralize IL-4 with the claimed dissociation constant.

18. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Loh et al, Nature vol. 276 p. 785 (1978).

This reference discloses the amino acid sequence of light chains are comprising amino acid sequences comprising Seq ID No 16 and 18 of the instant invention (Figure 2).

19. Claims 1-4, 7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Perfetti et al. Molec. Immunol. vol. 287 p. 505 (1991),

This reference discloses the amino acid sequence of the heavy chain as containing thr-ser-gly-met-gly-val-ser (corresponds to SEQ ID No. 22 of the instant application) (Fig. 3) and the production of said heavy chain using recombinant technology.

20. Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by Ramanathan *et al* (WO/91/09059).

Ramanathan *et al* teach mouse monoclonal antibodies produced by immunization with a peptide corresponding to residues 61-82 of human IL-4 (See page 26). The ability to neutralize IL4 is deemed to be an inherent characteristic of the referenced antibodies in view of the showing that polyclonal antibodies elicited against the same peptide immunogen blocked binding of human IL-4 to its receptor. A dissociation constant of less that 2×10^{-10} M is deemed to be an inherent characteristic of the referenced antibodies given that most monoclonal antibodies have affinity constants of 2×10^{-10} or less.

21. Claims 30 ~~and 33~~ are rejected under 35 U.S.C. 102(b) as being anticipated by JP-327725.

JP-327725 (Derwent Publ. Ltd. Abstract 91-284372) teaches high affinity mouse monoclonal antibodies specific for human IL-4 which neutralize IL-4 activity and a method for detection of IL-4 comprising the steps of contacting a biological fluid with monoclonal antibody and assaying for the occurrence of binding of antibody and IL-4 (See sections 3 and 11). No distinctions are seen between the claims and the reference.

22. Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by Chretien *et al.* J. Immunol. Methods vol. 117 p. 67 (1991).

Cretien *et al* teach rat monoclonal antibody 11B4 which inhibits the TCGF bioactivity of human IL-4 (See page 76) A dissociation constant of less than 1×10^{-10} M is deemed to be an inherent characteristic of the referenced antibody given that most monoclonal antibodies have affinity constants of 1×10^{-10} mol^{-1} or less.

Claim Rejections - 35 USC § 102/103

23. Claims 1 and 32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ramanathan *et al* (WO91/09059) or JP-327725 or Cretien J. Immunol. Methods vol. 117 p. 67 (1991).

The teachings of Ramanathan, JP-327725, and Cretien are set forth above.

The invention of claim 1 is characterized as a fusion protein. However, given the lack of specified structural elements in the claims to distinguish the claimed fusion proteins from those that would be produced by hybridomas as disclosed in the cited references. The claimed fusion protein is deemed to be the same as the monoclonal antibodies taught in the prior art.

Although the reference appears to disclose the same product claimed by applicants, the reference does not disclose the products produced by the claimed process. However the purification of production of a product by a particular process does not impart novelty to a product when the product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner.

See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972).

Therefore even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art.

See In re King, 107 F. 2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F. 2d 599, 601, 38 USPQ 143-145 (CCPA 1938); In re Bergy, 563 F. 2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) vacated 438 US 902 (1978); and United States v. Ciba-Geigy Corp, 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

Even if the prior art antibodies are not identical to those instantly claimed, given the teaching of the prior art specifically characterizing the anti-IL-4 antibodies in combination

with conventional hybridoma methods if would have been *prima facie* obvious to produce similar antibodies having the same specificity and function. One of ordinary skill in the art would have expected to obtain antibodies having the claimed affinity, since affinity constants for antigen-antibody binding within the range of 10^5 mol^{-1} to greater than 10^{10} mol^{-1} are commonly observed. It would have been *prima facie* obvious to apply well established immunoglobulin gene cloning and expression methods to produce fusion proteins such as chimeric antibodies, having variable regions of the antibodies suggested by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

24. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

25. Claims 1-4, 14-17 and 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen *et al* (WO 90/07861) in view of Abrams *et al* US 5041381, Chretien *et al* J. Immunol. Methods vol. 117 p. 67 (1991) and Curtis *et al* US 5108910.

Queen *et al* teach methods for producing fusion proteins which are chimeric or CDR grafted humanized antibodies. The reference describes an approach for producing CDR grafted antibodies which involves the selection of human variable regions which are homologous to the murine variable region to be humanized and computer modeling to identify murine framework residues which make key contacts with CDRs, which are then introduced into human frameworks (see abstract, p. 4-6 10-11). This reference also teaches that the art recognizes that humanized antibodies are expected to have advantages for use *in vivo* human therapy applications (p. 3).

The only difference between this invention and the reference is the specificity of the antibody, pharmaceutical compositions and the advantages of using a fusion protein linked to an additional peptide.

Abrams *et al* teach rat monoclonal antibody 1C1.11B 4.6 which has specificity for human IL-4. Abrams further teaches of compositions containing a therapeutic amount of at least one monoclonal antibody in a pharmaceutically effective carrier. (See column 6 lines 55-60).

Curtis *et al* teach of the advantages of an amino acid sequence of the fusion protein being linked to an additional peptide. This peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody. Curtis concludes that this second fusion to the original protein is superior over the original fusion protein of Granulocyte Macrophage Colony Stimulating Factor and Interleukin 3 alone. (See Column 7)

Chretien *et al* teach neutralizing anti-IL-4 monoclonal antibody 11B4 which has use in immunoenzymatic assay, immunopurification and potential implications in certain pathological conditions.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce mouse or rat neutralizing monoclonal antibodies such as those described in the secondary references. A large proportion of such antibodies would have been expected to have dissociation constants of 1×10^{-10} or less. Having obtained murine neutralizing antibodies, it would have been obvious to apply methods such as those taught

by Queen *et al* in order to develop fusion proteins which are chimeric antibodies having murine variable regions and human constant regions or humanized antibodies comprised of mouse CDRs fused to framework sequences derived from human antibodies having variable regions with high homology to the murine antibodies to be humanized. It would have been further *prima facie* obvious to include a pharmaceutically acceptable carrier as taught by Abrams, and to include a second fusion partner as taught by Curtis *et al* for the purpose of increasing the desired effects.

26. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 91/09059 or Chretien *et al* J. Immunol. Methods vol. 117 p. 67 (1991).

Both references disclose screening procedures (ELISA) for anti-IL-4 antibodies (p. 16 of WO and p. 69 of Chreiten et al).

The only difference between the reference and the instant invention is the use of aldehyde-coupled or biotinylated IL-4.

The use of biotinylated agents in ELISA is well known in the and therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to biotinylate IL-4 and use it in an ELISA screening assay. It is noted that the ELISA of Chreiten et al is an indirect assay not a direct assay. The use of either an indirect assay or a direct assay is within the purview of one skilled in the art.

Conclusion

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US 5597710 Dalle et al.

28. No claim is allowed.

29. Claim 18 is free from the art of record because the prior art does not enable the use of a monoclonal antibody to treat IgE related disorders. Therefore, WO 89/06975 is not enabled for the method claim.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is (703) 305-7866. The examiner can normally be reached on Monday-Thursday from 6:30am to 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703)308-2731. The FAX phone number for this Group is (703)308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Sheela J. Huff
May 2, 1997

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